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**Sham or real – post-hoc estimation of stimulation condition in a randomized
transcranial magnetic stimulation trial**

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Abstract

Selecting a suitable sham condition within the frame of repetitive transcranial magnetic stimulation (rTMS) treatment trials is a central issue. On the one hand, the ideal sham condition should not have a real stimulation effect; on the other hand, it should not be recognized as sham by patients, particularly when considering that real stimulation conditions come along with rTMS specific side effects. Within the course of a multicentre trial assessing the antidepressant effects of rTMS, patients were randomized to sham or real stimulation, in both cases using a standard stimulation coil. In one centre, patients (n=33) were asked about their impression whether they received the sham or the real treatment, and if they would recommend the treatment to others. 29 patients returned the questionnaires and were included into the analysis. From 15 subjects with real stimulation, 11 suggested to have obtained real, and 4 to have obtained sham. From 14 sham stimulated subjects, 9 suggested to have obtained the real condition and 5 to have been sham stimulated. This difference was not significant ($p=0.60$, chi square test). In addition, the major part of patients in both stimulation conditions would recommend rTMS to others. In both conditions, real and sham, the majority of subjects believed to have obtained the real condition. This implies suitability of the sham condition used since subjects appeared not to be able to identify the condition. The results imply the feasibility of a valid sham condition with a “real” coil.

Keywords: Transcranial magnetic stimulation, treatment trials, depression, sham condition

Introduction

Major depression belongs to the leading causes of disease burden worldwide [4]. Repetitive transcranial magnetic stimulation (rTMS) was introduced as a promising treatment option for depression and showed beneficial but at most moderate effects in single- and multi-centre trials [7, 10, 11, 13, 18, 19]. Its application in depressed patients had recently been approved by the U.S. Food and Drug Administration and it is increasingly offered in psychiatric services. However, till now it remains difficult to draw consistent conclusions about the antidepressant efficacy of rTMS based on present publications. This is firstly due to inconsistent results, secondly due to methodological issues [8, 16, 19]. A primary issue, evident in each randomised stimulation trial, is the sham condition. On the one hand, real stimulation and sham stimulation have to be different concerning their efficacy: real should cause an effective stimulation, sham should not. On the other hand, sham and real should not differ concerning the subjective experience of the stimulation. The first aspect can be fulfilled by dislocating the coil or using a so called “sham coil”, the second one by inducing the characteristic noise and the sensory, sometimes painful artefact [5]. That sensory artefact however, is not present when using commercially available sham coils or it is of a different character when attempting to mimic the sensory impression [2]. Further, it is impossible to blind the experimenter because he or she has to apply the stimulation and has to know how and where to do that. The term “double-blind”, within rTMS trials, thus refers only to patient and rater, who are unaware of the stimulation condition. Still, the experimenter might have an unintentional influence on the patient. Since stimulation conditions have to be different between each other to establish sham and real, the patient, too, might identify the applied condition. Accordingly, in randomised controlled trials (RCTs) the question often arises whether patients are able to guess their treatment condition. In the present study we aimed to clarify whether patients participating an rTMS RCT would be able to successfully guess which kind of stimulation they received: sham or active. Additionally, we also considered interesting to know whether the patients believed to benefit from the stimulation and would recommend the stimulation to others, and whether their expectation towards the stimulation might have biased treatment outcome.

Methods

Study design and participants

Within the frame of a randomised, double-blind, placebo-controlled, multi-centre trial to assess the antidepressant effect of rTMS [11], the patients within one centre (Ulm, n=37, 4 drop-outs, 33 completed the treatment trial, 29 of these returned the questionnaires, fig. 1), were asked in the weeks afterwards by a questionnaire about their experience of rTMS, particularly concerning the stimulation condition. All patients gave written informed consent. The trial was performed according to the latest version of the Declaration of Helsinki and was approved by the local ethics committee. Inclusion criteria were: age 18-75 years, a moderate or severe major depressive episode according to ICD-10 and DSM-IV and a score of 18 points or more in at least two of the three depression rating scales: Becks' Depression Inventory (BDI) [3], Hamilton Depression Scale (HAM-D 21-items version) [9], Montgomery-Åsberg Depression Rating-Scale (MADRS) [17]. The detailed methodology with exclusion criteria and add-on design onto parallel established antidepressant medication and the clinical results of the trial were reported earlier [11]. Included patients were given an identification number linked to a centralised computer-generated randomisation code determining real or sham stimulation condition.

Transcranial magnetic stimulation – real and sham condition

A magnetic stimulator with a figure-of-eight coil was used for rTMS (Medtronic Magpro; Medtronic Inc., Minneapolis, MN, USA; coil: MC-B70). Patients were seated in a comfortable chair during stimulation. Stimulations were performed with a frequency of 10 Hz, trains of 2 seconds, inter-train-intervals of 8 seconds, 100 trains per session, 2000 stimuli per day on 15 subsequent working days. The real stimulation was applied above the left dorsolateral prefrontal cortex (DLPFC), targeted by guiding the coil to the position F3 according to the International 10-20 system for electroencephalography electrode placement [12]. The real stimulation intensity was determined as 110% of the individual resting motor threshold (MT) [22]. Sham stimulation was applied 5 cm lateral to F3, perpendicular to the parasagittal plane, above the left temporal muscle.

To reduce a possible effectiveness of sham stimulation, the coil was angled at 45°, touching the skull not with the centre but with the rim opposite the handle, and the stimulation intensity was reduced to 90% MT. In this position, the coil-cortex distance also is essentially larger (more than 3 cm versus 1-1.5 cm) than above F3, such that the electromagnetic field, if at all reaching the cortex, due to technical reasons was substantially weaker and far outside the target region.

Questionnaires and statistics

Within the weeks after the antidepressant stimulation, all patients that completed treatment in the centre should answer and return a questionnaire concerning their experience with rTMS, with a particular focus on the stimulation condition. If patients did not return the questionnaire upon the estimated time of four weeks, they were contacted by phone and asked the same questions. The following questions were posed (original in German, here English translation):

- a. Which expectation did you have concerning successful treatment prior to rTMS? Range 1 to 4, with 1 being no, and 4 being very high expectations
- b. Two stimulation conditions were possible, real and sham, which one do you think you received? Sham/real
- c. Would you recommend rTMS treatment to others? Yes/no
- d. Did you have the impression that rTMS overall helped you? Yes/no

Treatment outcome dependent on treatment conditions as measured with the three rating scales was analysed with Mann-Whitney U-test due to non-parametric distribution. In order to assess (i) whether the patients estimated to have received real or sham stimulation, (ii) whether they would recommend rTMS, and (iii) how they felt after rTMS, the data were analyzed with a chi square test. The hypothesis was that 'real' and 'sham' should not be discriminated by the patients as reflected in comparable amounts of estimations with no statistical differences concerning the questions of guessing the condition and of recommendation (assuming that one would not recommend a treatment not considered to be effective). To assess the influence of expectation on treatment

outcome irrespective of condition, we pooled the groups with low and medium low expectation vs. high and medium high expectation into two groups and subjected the data to a chi square test.

Results

From 37 patients that were enrolled in the centre, 33 completed stimulation. Within this group responses from 29 patients, i.e. 88%, were obtained, 4 patients did not answer (fig. 1). These 29 were included in further analyses (demographic data in table 1). They responded to all questions except the question concerning recommendation which was not answered by 4 patients. Regarding the antidepressant treatment outcome, the patients did not show significant differences between real and sham in all three scales, whenever one might observe a descriptive improvement particularly of HAM-D and BDI scores (table 1). Concerning the HAM-D score, the sham group was slightly less depressed prior stimulation than the real group which was not the case in BDI and MAD.

Regarding whether patients considered real to be real and sham to be sham, from 15 real stimulated patients, 11 suggested to have received real, and 4 sham. From 14 sham stimulated patients, 9 also estimated to have received the real condition and 5 to have been sham stimulated (table 1). This difference was not significant ($p=0.60$, chi square test). Further, the majority of patients in both stimulation conditions would recommend rTMS to others: 10 out of 15 'real', and 9 out of 14 'sham' stimulated patients. Higher expectation towards rTMS concerning improvement of depression did not result in better treatment outcome than lower expectations (table 1).

Finally regarding the question whether the patients had the subjective impression that rTMS was effective or not, 11 of the 15 real stimulated patients got this impression (73%), and 5 of the sham stimulated patients (36%), which represented a significant difference ($p=0.042$, chi square).

Discussion

Regarding the crucial issues of blinding in rTMS treatment trials and of using a control condition to test against the real one, the aim of the study was to assess whether patients that were randomized to real or sham stimulation in an antidepressant treatment trial would guess the applied

stimulation condition. The main finding was that patients did not identify the sham stimulation condition as such. In both groups a comparable majority of patients estimated the stimulation to be real. On the other hand, a considerable amount of patients in the real condition thought the condition to be 'sham'. The result of non-identification of sham is also supported by the finding that the major part of patients would recommend rTMS as treatment strategy in depression, and this result was obtained irrespective of the stimulation condition. Concerning the clinical outcome as measured with the rating scales, no advantage in rTMS response was observed due to the 'real' condition apart a descriptive improvement. This is in line with the overall results of the multicentre trial [11]. However, and interestingly, when being asked whether they had the general impression of having benefited from rTMS, a majority of real stimulated patients had this impression but only a minority of the sham group. This is of course no hard criterion; nevertheless, it was significant and may be taken to indicate sort of a subjective effect. This points also to a less to a placebo effect of the sham condition, because in case of a placebo effect both groups should have had a comparable subjective effect of sham and real. However, with our add-on design comprising standardized medication, a statement on a possible placebo effect is difficult [6].

Finding a valid sham condition in TMS research and particularly in RCTs is of key importance for producing valid outcomes [2, 14]. Considering the facts that the experimenter can not be blinded (unlike the rater) and the patients may either detect that they received an untypical stimulation because they are informed about TMS or because of less or no sensory side effects in relation to the sham stimulation, the probability of guessing the condition should be high. Several strategies have been proposed to address this issue. These can be divided in two principal strategies: First, by modifying a real stimulation in a way that it is ineffective (e.g. [11]), for instance by reducing the intensity, angling the coil or dislocating the coil. Secondly, it can be done by applying a special sham coil (e.g. [18]). In both strategies, the issue of the side effects of rTMS are to be considered. These are particularly the acoustic artefact and the local sensory artefact. The acoustic artefact is present in both strategies. The sensory artefact is not present or has to be technically simulated with the sham coil [5], or it might be critically diminished when modifying a real stimulation to be

ineffective. In our rTMS multi-centre trial, a modified stimulation condition for sham was chosen. We combined the three possibilities of angling and dislocating the coil and reducing the stimulation intensity. Whenever angling of the coil might be registered by the patients to be a different coil handling as when measuring the motor threshold, this was a compromise made for attempting to apply a sham condition largely similar to real but with as less as possible efficacy. Because of the dislocation towards direction of the temporal muscle, the coil-cortex distance was conceivably higher (>3cm concerning anatomical evaluation with frameless stereotaxic visualizing) than above the prefrontal cortex. Further, due to angling the focus of the magnetic field was not directed towards the skull but just in the air. Due to the resulting substantially weaker electromagnetic field that might have reached the cortex largely outside the target region in this condition compared to real rTMS, a possible neuronal depolarisation [14, 15] was unlikely, as was any possible antidepressant effect. Nevertheless, this kind of sham stimulation had disturbing effects by local sensations above the temporal muscle, which was directly touched with the rim of the coil, due to stimulation, that were similar to the disturbance caused by the real stimulation [1, 20]. Using a sham coil with no stimulation would have been even more different to real stimulation considering the lack of local sensations compared to the experience of motor threshold determination. Newer developments of devices that for instance provide a sensory artefact by electrical stimulation are not (yet) available for standard use and cannot reproduce the effects of magnetic stimulation exactly [2, 21]. Our findings suggest that the “real” coil with the described modifications can be used for a reliable and simply applicable sham condition in randomized rTMS trials, and they support the validity of the results from this methodological point of view.

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Conflicts of interest: All authors declare that they have no conflicts of interest.

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Table 1: Demographic and clinical data of included patients.

	Real	Sham	sign., p
N	15	14	
Age m/sd	51.1 / 12.1	52.6 / 13.4	n.s. (0.74)
Gender	7m / 8f	5m / 9f	n.s. (0.36)
BDI pre m/sd	29.9 / 9.4	32.0 / 7.3	n.s. (0.50)
HAM pre m/sd	24.3 / 3.9	21.1 / 4.1	0.036
MAD pre m/sd	29.1 / 3.8	27.8 4.9	n.s. (0.43)
BDI diff m/sd	-14.9 / 9.2	-10.6 / 11.4	n.s. (0.25)
HAM diff m/sd	-13.7 / 7.5	-10.5 / 8.2	n.s. (0.29)
MAD diff m/sd	-16.5 / 7.8	-14.9 / 8.5	n.s. (0.91)
Co venlafaxine	8	7	n.s. (0.86)
Co mirtazapine	7	7	
Consid. real n (%)	11 (73%)	9 (64%)	n.s. (0.60)
Consid. sham n (%)	4 (27%)	5 (36%)	
Recom. Yes n (%)	10 (67%)	9 (64%)	n.s. (0.16)
Recom. no/miss. (%)	5	5	
Benefit yes	11 (73%)	5 (36%)	0.042
Benefit no	4 (27%)	9 (64%)	

Abbreviations: m mean, sd standard deviation, diff difference pre-post, co co-medication, consid. consideration (question 1), recom. recommendation (question 2), miss. missings

Statistics: t-test for age, Mann Whitney U test for rating data, Chi square test for categorical data.

Figure

Figure 1 Diagram illustrating the inclusion of patients in questionnaire assessment.

